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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/810,670	03/19/2001	Akiko Itai	P20797	9032

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EXAMINER

MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No. 09/810,670	Applicant(s) ITAI ET AL.	
	Examiner Marjorie A. Moran	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 October 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 6, 7, 11-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 6, 7 and 11-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>6/8/06</u> . | 6) <input type="checkbox"/> Other: _____ |

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. All rejections and objections not reiterated below are hereby withdrawn. Claims 1, 6, 7 and 11-13 are pending.

Information Disclosure Statement

The IDS filed 6/8/06 has been considered in part. It is unclear which of the many applications listed under citation number 6 is to be considered, therefore the entirety of citation #6 has been crossed out. If applicant wishes to have the WO document considered, then it is noted that the WO document has been considered as it was properly cited under "Foreign patent documents."

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 6, 7, and 11-13 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are directed to a method for selecting lead-candidate compounds capable of binding as a ligand to a protein. The claim steps recited are all in silico steps; i.e. steps of mathematical manipulation. The claims do not recite a physical transformation of matter.

Amended claim 1 now recites a step of "selecting" compounds; claims 6 and 7 recite steps of "screening" compounds. A step of selecting is not a physical

transformation of matter. The "screening" steps of claims 6 and 7 are interpreted to be in silico steps in light of the specification and therefore are not considered a transformation of matter from one form or state to another. Where a process claim does not recite a physical transformation of matter, it may be statutory where it recites a practical application; i.e. a concrete, tangible and useful result. While the *result* of a "selecting" or "screening" step may be concrete, it is noted that the claims do not actually recite a result of selecting or screening. Further, no result is communicated to user or otherwise "output" in a tangible form useful to one performing method, therefore the claims fails to recite a concrete, tangible and useful result. For a further discussion, applicant is referred to MPEP 2106, especially section IV.

Applicant's arguments filed 11/7/06 have been fully considered but they are not persuasive. Applicant argues that the Office has misapplied the Utility guidelines. In response, it is noted that the rejection is made over non-statutory subject matter, NOT lack of utility. Applicant is reminded that utility guideline are set forth in MPEP **2107** while guidelines with regard to statutory subject matter may now be found in MPEP **2106**. While both utility and statutory consideration fall under the same statute, the considerations for each are different, as reflected in the different sections of the MPEP. The examiner maintains that she has indeed applied the *statutory* guidelines as set forth in MPEP 2106 properly. Applicant appears to agree that a recited RESULT must be concrete, tangible and useful, as set forth on page 7 of the response, but then sets forth only reasons why the claims are useful. The previous rejection with regard to *nonstatutory* subject matter stated that the claimed "result" was neither concrete nor

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tangible. Applicant does not set forth any arguments with regard to a concrete and tangible result. The examiner maintains that the claims do not recite any concrete or tangible result for the reason previously set forth and reiterated above. Thus, the arguments are not convincing.

As the claims do not recite a physical transformation or a **concrete, tangible** and useful result for the reasons previously set forth and set forth above, the rejection is maintained.

35 USC § 112, 1st para.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 7, and 11-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following includes both a lack of enablement and a lack of scope of enablement rejection.

The claims are not enabled for SELECTION of a lead-candidate compound which binds to any type of biopolymer because neither the specification nor the prior art teach specific parameters for selection of a compound or compounds which bind to any (generic) biopolymer.

The factors to be considered in determining what constitutes undue experimentation were affirmed by the court in *In re Wands* (8 USPQ2d 1400 (CAFC 1986)). These factors are the quantity of experimentation; the amount of direction or guidance presented in the specification; the presence or absence of working examples; the nature of the invention; the state of the prior art; the level of skill of those in the art; predictability or unpredictability of the art; and the breadth of the claims.

The claims are quite broad as they are directed to selection of a lead-candidate compound capable of “binding as a ligand” to a protein. The specification teaches, in examples, how to determine/identify compounds likely to bind to a protein, specifically dihydrofolate reductase. However, the specification does not teach particular conditions which must be met to select a compound as a “lead-candidate”; i.e. to single out any particular compound as being a “better” ligand than the others, or which binds more tightly than another, etc. The state of the prior art is such that docking programs for “fitting” a ligand into a binding site of a protein are known. See e.g. DESJARLAIS et al. (IDS ref: J. Med. Chem. (1988) vol. 31, pp. 722-729). DESJARLAIS teaches specific steps for “scoring” the fit between a receptor and candidate compounds and teaches on page 724 that a user may “select the number of top scoring candidates” to be saved for further energy minimization steps. It is noted that the claimed methods do not recite any particular steps of scoring or ranking candidate compounds similar to those of DESJARLAIS, such that a selection may be made of the “top” or “lead” candidates. Amended claim 1 recites “judging similarity” of partial structures of a query molecule and a trial compound, but fails to recite any parameters for “judging similarity” nor

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selection of compounds which are "most similar" or any other selection which indicates that a structure is a "lead" compound. The instant specification does not disclose any parameters or specific steps for "judging similarity" such that a "lead" compound may be selected. The prior art of NISHIBATA (IDS ref: Tetrahedron (1991) vol. 47, no. 43, pp. 8985-8990) teaches specific parameters for selection of nine "lead-candidate" structures from among the 300 possible structures generated (pp. 8987-8989). The instant specification does not provide any such parameters or any other information to determine whether a compound is a LEAD compound. Amended claim 1 recites matching modes of covalent bonds but fails to disclose any specific parameters which would allow one of skill in the art to know what degree, if any, of similarity is required for a "match" in order for similarity to be "judged" nor does the specification teach how to determine whether a particular compound is a LEAD compound based on the matching. Neither the instant claims nor the specification disclose which parameters are to be used to determine "matching".

The level of skill in the art of docking/fitting is acknowledged to be high. Despite this, it would require undue experimentation for one of skill in the art to determine how to *select* a "lead-candidate" capable of binding to a protein or any other type of biopolymer because neither the specification nor the prior art teach conditions or parameters for determining the "best" or "lead" compounds from a compound database. Determination of a "lead" compound depends on which algorithm is used, what type of protein is chosen, and what type of activity one is looking for in a "lead" compound. As

one of skill in the art would have to guess at the parameters involved in selection and/or “matching” to a query molecule, this would require undue experimentation.

For the reasons set forth above, the claims are not enabled for selection of **lead-** candidate compounds of any type, as previously set forth and reiterated above.

Applicant's arguments filed 10/4/06 have been fully considered but they are not persuasive. Applicant argues that the amendment reciting a “protein” overcome the enablement rejection. While the amendment does overcome the part of the enablement rejection regarding ligands for “biopolymers,” it does not overcome the rejection with regard to selection of LEAD compounds for the reasons set forth above. For these reason sand those previously set forth, the rejection is maintained.

Claim Rejections - 35 USC § 112, 2nd para.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6, 7, and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a method for selecting a lead candidate compound in the preamble. Step (a) recites choosing a query molecule then step (b) recites selecting lead-candidate compounds by matching bonds between the query molecule and a “trial compound.” It is unclear whether the “trial compound” or the “query molecule” (or neither) is intended to be the lead-candidate compound. If neither, then it is further

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unclear what relationship, if any, the lead-candidate molecule has to either of the query molecule or trial compound. As the limitation intended for a lead-candidate compound is unclear, claim 1 is indefinite.

Amended claims 6 and 7 recite the term "the compounds", each in lines 2-3. The antecedent basis for "the compounds" is unclear as parent claim 1 recites several different compounds, therefore claims 6 and 7 are indefinite. If applicant intends that the database comprise 3D structures for the compounds in the database only, then this rejection may be overcome by inserting --in the database-- after "compounds" in line 3 of each claim.

Claims 6 and 7 recite that "the compound database comprises" 3D information "and which further comprises:" followed by steps. This is confusing as it appears that applicant is limiting the database to comprise method steps, thus the claims are indefinite. If applicant intends to further limit the database to one comprising 3D structural information and to limit the method to comprise further method steps, then this rejection may be overcome by replacing "which" with --wherein the method-- before "further comprises" in line 3 of each claim.

Claims 6 and 7 recite a step (e) of "screening" lead-candidate compounds but fail to recite what the compounds are screened for, or against. As the parameters required for screening are unclear, claims 6 and 7 are indefinite.

Claim 6 recites the limitation "the lead candidate compound" in the first line of step (c) and in step (d). There is insufficient antecedent basis for this limitation in the claims, therefore claim 6 is indefinite. Parent claim 1 recites selecting lead-candidate

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compounds (plural) in step (b) but nowhere recites selection of a single lead-candidate compound.

Claim 6 recites a step (c) of estimating ... "and binding scheme to the protein of the query molecule" which is nonsensical. It appears that a term or terms are missing. As it is unclear what step or other limitation is intended by the phrase, the claim is indefinite.

Claim 6 recites, at the end of step (c), the phrase "based on correspondence of the partial structures of the query molecule and the (trial) compound." It is unclear what is intended to be "based on" correspondence of the molecule and compound, therefore the claim is indefinite. It is also unclear what degree of similarity is required in order for something to be "based on" a "correspondence", therefore the claim is further indefinite.

Claim 7 recites that something is "based on" information of three-dimensional structures, in lines 2-3 of step (c). It is unclear what is intended to be "based on" the 3D information; i.e. the receptor model, the physiochemical environment, the ligand binding site, or the entirety of the estimating step. It is further unclear what parameters must be included or what relationship is intended between elements in order for the (something) to be "based on" 3D information. For these reasons, claim 7 is indefinite.

Claims 11-13 recite a step of "further ...constructing the structure.." It is unclear where or when in the method of claim 1 the constructing step is intended to occur, and what relationship this step is intended to have with any other method step, therefore claims 11-13 are indefinite.

Applicant's arguments filed 10/4/06 have been fully considered but they are not persuasive. Applicant argues that the amendments overcome the rejections of record. However, all rejections above are based on the claims as amended, therefore the arguments are moot.

Claim Rejections - 35 USC § 102

Claims 1, 6, 7 and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by WANG et al. (IDS ref: J. Med. Chem. (1994) vol. 37, pp. 4479-4489).

Applicant's arguments with respect to claims 1, 6 and 7 have been considered but are moot in view of the new ground(s) of rejection.

WANG teaches a method of selecting lead-candidate compounds which act as ligands for a protein (PK-C) comprising searching a database of 3D structures for compounds which match a query compound (p. 4480: Results). As WANG teaches that his 3D information includes types and lengths (modes) of covalent bonds (p. 4480: para spanning bottom of left column-right column), his matching of 3D structures inherently includes matching modes of covalent bonds., thus claim 1 is anticipated. WANG teaches estimating binding of selected compounds to his protein in modeling studies, and choosing those pharmacophores which have the best "match" to a model pharmacophore or which "fit" best into the protein binding site (p. 4485-6). WANG teaches that his compounds may be further screened in competition assay (p. 4486, right column), therefore claims 6 and 7 are anticipated. WANG teaches automatic

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structure construction programs for his query molecules (p. 4480: D), thereby anticipating claims 11-13.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 6/8/06 also prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571) 272-0720. The examiner can normally be reached on Monday-Friday; 6 am-2:30 pm EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marjorie A. Moran
Primary Examiner
Art Unit 1631

Marjorie A. Moran
12/11/06